REMARKS

Claims 23-42 are pending in the application.

I. Rejection Under 35 U.S.C. § 103(a) as Being Unpatentable Over Coleman in View of Grabarek and Wong.

The Examiner has maintained the rejection of claims 23-26, 29-32, and 34-42 under 35 U.S.C. § 103(a) as being unpatentable over the combination of Coleman, Grabarek, and Wong. The Examiner contends that Coleman teaches use of FIBREL, containing porcine gelatin powder, mixed with a patient's plasma and ε-amino caproic acid, wherein the FIBREL is an injectable material for soft tissue augmentation. The Examiner states that the Coleman composition contains "cross-linked, blood plasma proteins," but does not provide support for this statement. The Examiner merely states that "mixing the patient's own plasma with gelatin powder and ε-amino caproic acid ... is a clear indication that cross-linkage of a blood plasma protein has occurred in the reconstitution step for the FIBREL to be useful for filling depressed defects in a patient." Office Action at page 4. However, no technical or logical basis for this conclusion is provided. The statement remains unsupported.

The Examiner concedes that Coleman does not teach cross-linkages that are accomplished using zero-length cross-linking agents and procedures. However, he supplies Grabarek to allegedly remedy this deficiency. Wong is applied for its disclosure of various zero-length cross-linking reagents for the purpose of inducing the direct joining of, and creation of stable bonds between two intrinsic chemical moieties of one or more polypeptide chains without the introduction of any extrinsic matter.

On this basis, the Examiner reasons that a person of ordinary skill in the art would have been motivated to make the combination proposed by the Examiner.

The applicants respectfully traverse the rejection, for the reasons given below. In presenting these reasons, the applicants rely upon the Declaration of Rozlyn Krajcik previously submitted on July 9, 2003.

Coleman teaches a composition for treating wrinkles and scars that contains a mixture of porcine gelatin powder (collagen), sterile saline, and ε-amino caproic acid. The mixture is sold

under the tradename "FIBREL." When administered, Coleman teaches that FIBREL may be mixed with a patient's plasma prior to injection. Coleman teaches that FIBREL was designed to stimulate collagen production by the patient's own cells at the site of injection. Col. 1:22-23. Coleman also discloses that use of the composition without the addition of the patient's blood plasma is as effective as use of the composition that does contain the blood plasma. In fact, Coleman advises that use of FIBREL without the blood plasma is additionally advantageous, as it avoids any chance of inadvertent contamination of the physician or the physician's assistant with the blood plasma mixture during mixing. Col. 1:37-41. Coleman does not teach or suggest that the blood plasma that may be used to reconstitute the FIBREL powder contains blood plasma proteins that have any cross-linkages at all, let alone cross-linkages comprising at least one amide bond.

Grabarek teaches a two step procedure for zero-length cross-linking using active esters. Wong teaches various zero-length cross-linking reagents for the purpose of creating stable bonds between two intrinsic chemical moieties or one or more polypeptide chains.

The combination of Coleman with Grabarek and Wong does not render obvious the claimed invention. The application of the combination of Coleman-Grabarek and Wong does not satisfy all of the requirements for establishing a *prima facie* case of obviousness. First, there is simply no teaching of cross-linked blood plasma proteins of any kind in any of the three cited references, including Coleman. The Examiner, while insisting to the contrary, has provided no explanation or basis for the assertion nor has he cited to any specific portion of Coleman that lends support to this proposition. He has merely stated that it is "clear[ly] indicate[d]." Such lack of support is not surprising as Coleman does not teach use of cross-linked blood plasma proteins.

Coleman merely discloses use of FIBREL, a composition which uses the connective tissue protein collagen to fill depressed defects. As disclosed in Coleman, the FIBREL composition is made of porcine gelatin (a collagen) and ε-amino caproic acid. The FIBREL composition itself does not contain any blood plasma proteins. As is known to one of skill in the art, a collagen is not a blood plasma protein, but is rather any of a group of fibrous proteins that form the main component of connective tissue in mammals. *See,* Specification at page 8; Dec. of Rozalyn Krajcik at ¶ 26. E-amino caproic acid is not a protein at all.

Notably absent from Coleman is any suggestion or teaching that the collagen in the FIBREL is cross-linked. Indeed, as pointed out in prior responses, other prior art cited by the Examiner concerning FIBREL expressly teaches that the "mode of action of FIBREL involves the activation of the patient's own fibroblasts and subsequent collagen deposition by those cells, *i.e.*, deposition of host collagen, which production and/or deposition at the target augmentation site is induced by the FIBREL injection. Pollack at col. 1, ll. 28-32. *See also*, Coleman at col. 1, ll. 22-23.

Moreover, there is no teaching in Coleman that any proteins that may be present in the blood plasma used to reconstitute the FIBREL composition are cross-linked in any manner. There is no factual or technical basis that would have caused a person of skill to believe that the blood plasma used in the reconstitution step described in Coleman inherently teaches plasma having amide cross-linked blood plasma proteins. These linkages are not spontaneously formed in solution, as is known to a person of skill in the art. Coleman does not discuss any process by which such cross-links would have been formed in the collected blood plasma. Dec. at ¶ 26. Coleman does not teach that the blood plasma to be used for the reconstitution of FIBREL is treated in any way so as to induce, encourage, or facilitate the formations of cross-linkages that include amide bonds. Coleman merely states that the blood plasma is mixed with the FIBREL powder to reconstitute it, and, moreover, states that use of the blood plasma itself is unnecessary. Dec. at ¶ 25.

Applicants have previously submitted the physician package insert that accompanies the FIBREL product for the Examiner's review. Dec. at ¶ 20. The package insert serves as confirmation that the blood plasma used in the reconstitution of FIBREL as taught in Coleman and Pollack is not treated or otherwise subjected to any processes that would result in the formation of amide cross-linkages of any constituent blood plasma proteins, or any other type of cross-linkages. Dec. at ¶ 27. In fact, one of skill would understand that any formation of linkages in the blood plasma is discouraged. The package insert discloses that the anti-coagulant citrate dextrose is added to the blood plasma sample to prevent blood coagulation. Dec. at ¶ 27. Anti-coagulants are known in the art to prevent the cascade of enzyme-mediated reactions that result in clotting, *i.e.*, the formation of bonds between various blood proteins. Thus, Coleman, in providing this teaching, inherently discloses that the formation of cross-linkages between and among blood plasma proteins is in fact undesirable. Dec. at ¶ 27.

Furthermore, a person of skill in the art upon reading Coleman would understand that there are no amide bonds formed between the blood plasma proteins which may be present in the patient's plasma, as the formation of such bonds does not occur spontaneously and casually in nature. Dec. at ¶¶ 27-29. This fact is also demonstrated by the examples presented in the patent application itself. Dec. at ¶¶ 31-36. Attempts at tissue augmentation using blood plasma alone, as seen in Comparative Use Example 1, were unsuccessful, in comparison to tissue augmentation carried out using the composition of the invention. *See*, Table 1, comparing Comparative Use Example 1 to Use Example 1; Dec. at ¶¶ 33-35. The addition of Grabarek and Wong does not remedy these deficiencies. Grabarek does not teach or suggest compositions for use in tissue augmentation. Additionally, the proteins upon which the two step zero-length cross-linking procedure are practiced are obtained from rabbit back and leg muscles, and are not blood plasma proteins. In Wong, only a general disclosure of zero-length cross-linking procedures is provided. No discussion of use of these in cross-linking blood plasma proteins to prepare a tissue augmentation device is taught or suggested.

Additionally, a person of skill in the art would not have been motivated to make the combination proposed by the Examiner. Coleman teaches use of FIBREL for tissue augmentation. FIBREL, as described above, acts to fill by recruiting fibroblasts which then secrete collagen, which itself then serves as the filler substance that results in the apparent augmentation. No blood plasma proteins are involved in the augmentation aspect of the composition. Thus, a person of skill in the art would not have been motivated to take blood plasma proteins, a different type of filler from that taught in Coleman, and, moreover, proteins that are ordinarily soluble and biodegradeable within the body, and cross-link them in order to arrive at the present invention. Finally, a person of skill in the art would not have had a reasonable expectation of success in making the invention. Coleman teaches collagen as a filler substance, a collagen that is secreted by the patient's own cells. A person of skill in the art would have understood that blood plasma proteins, which are normally soluble and biodegradeable, do not serve any cell signaling or recruiting function, are not capable of recruiting fibroblasts to enable secretion of collagen, and provide the subsequent "filling" of the intradermal skin compartment into which the composition is injected. A person of skill in the art reviewing Coleman and the secondary references would have had not reasonable expectation that the combination of these references would result in the tissue augmentation device that

comprises blood plasma proteins which are cross-linked, wherein the cross-linkages include at least one amide bond.

Accordingly, it is requested that the Examiner reconsider and withdraw the § 103(a) rejection.

II. Rejection Under 35 U.S.C. § 103(a) Over Coleman in View of Grabarek, Wong and Wang.

The Examiner has rejected claims 27, 28, and 33 under 35 U.S.C. § 103(a) as being unpatentable over the disclosure of Coleman, taken in view of Grabarek, and Wong, as applied to the claims listed above, and further considered in view of Wang. The Examiner contends that Wang reviews the various excipient (additives) and pHs for parenteral products in which the reference focuses on products with extreme pHs, and shows the tabulation of a pH range, acid or base used for adjustment, and product identities. According to the Examiner, the reference also discloses numerous physiologically acceptable fluids, such as additives for parenteral formulations, which include anesthetic compounds such as procaine. Therefore, the Examiner reasons that a person of skill in the art would have been motivated to combine the references listed above to arrive at the present invention.

The applicants respectfully traverse the rejection.

The disclosures of Coleman, Grabarek, and Wong, are given above and are incorporated herein by reference. The applicants note that Wang teaches physiologically acceptable fluids and additives for parenteral formulations.

The combination of the four references listed above does not render the invention of claims 27, 28 and 33 obvious for at least the reasons given above with respect to the prior rejection that did not include the disclosure of Wang. Moreover, a person of skill in the art would not have been motivated to combine Wang to prepare an invention for intradermal injection.

Accordingly, it is requested that the Examiner reconsider and withdraw the § 103(a) rejection.

III. The Non-Obviousness of the Claims is Supported by Secondary Considerations.

For the reasons discussed above, the Examiner has failed to demonstrate a *prima facie* case of obviousness. However, even if such case had been made, it is rebutted by the unexpected results achieved by the invention as described in all pending claims.

The tissue augmentation composition of the invention, once injected, lasts longer than the priority compositions that use collagen as does FIBREL, for the inventive composition is less rapidly degraded by the proteases and immune system components present in the human patient. Supporting data for this proposition can be seen at least in the specification at *e.g.*, Table 1 and Figure 1.

Table 1 compares the longevity of the filler masses produced by the composition of the invention (use example 1) and the collagen-containing prior art compositions (Comparative Example Uses 3 and 4). As is shown in Figure 2, when evaluated *in vivo*, the fillers of Comparative Uses 3 and 4 were almost completely degraded (average rating of 0.30) by day 526.

In contrast, the tissue augmentation composition of the invention was found to have an average rating of 3.019 by day 693. This demonstrates that the ability to withstand degradation and thereby function as a longer lasting augmentation device is substantially increased by the invention composition, in comparison to prior art collagen containing devices. Such results are unexpected, as both uncross-linked plasma proteins (Comparative Use 2) and cross-linked collagen (Comparative Use Example 3; ZYPLAST) exhibit relatively rapid degradation.

CONCLUSION

It is respectfully submitted that the claims are not obvious over the cited prior art. Accordingly, it is requested that the Examiner reconsider and allow the pending claims at the earliest opportunity.

Respectfully submitted,

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